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Abstract

Efficacy of the combined use of bevacizumab and irinotecan in a human colorectal cancer xenograft model analysed by SPECT imaging

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Introduction: Colorectal tumors are dependent on angiogenesis for growth and VEGF is a key mediator of tumor angiogenesis. Antiangiogenic drugs can induce a transient normalization of the tumor vasculature and can thus potentiate the activity of co-administered chemotherapy.

Aim: The efficacy of anti-human VEGF antibody (bevacizumab) with or without irinotecan was evaluated in a human colorectal cancer xenograft model.

Methods: Colo205-bearing mice were treated with a single dose (ip) of bevacizumab (5mg/kg) 2, 4 or 6 days prior to administration of a single dose of irinotecan (100mg/kg) or 0.9% NaCl. Microvessel density (MVD), collagen covered tumor vessels (Masson's Trichrome staining), pericyt coverage (α -smooth muscle actin immunostaining) and tumor hypoxic fraction (Pimonidazole staining) was determined at the three different time points following treatment of bevacizumab. To investigate the possible synergistic effects of the combination therapy, the apoptosis-detecting radiotracer ^{99m}Tc His-ann A5 was injected iv (0.5 mCi) in mice 12, 24 and 48 hours after start of the irinotecan treatment and also to control mice (n=3 in each time group). MicroSPECT imaging was subsequently performed 3.5 hours after injection of the radiotracer. The results were correlated to histological analysis for apoptosis (caspase-3 activation).

Results: MVD decreased significantly, α -smooth muscle actin and collagen covered vessels were increased compared to control tumors, 4 days after bevacizumab treatment, suggesting normalization of the tumor vasculature. Hypoxic fraction was slightly reduced 4 days after treatment with bevacizumab. SPECT analyses demonstrated a significant increase in tumoral ^{99m}Tc His-ann A5 uptake 4 days after bevacizumab treatment and 24h after irinotecan administration ($180 \pm 37\%$ injected dose/ tumor volume, $p < 0.05$) compared to each monotherapy demonstrating a synergistic effect of both therapies. Quantitative ^{99m}Tc -ann A5 tumor uptake correlated well with the number of apoptotic cells as determined by caspase-3 immunostaining ($R^2 = 0.81$, $p = 0.04$).

Conclusion: Four days after administration, VEGF inhibition with bevacizumab normalizes the tumor vasculature in the Colo205 model, leading to an improved cytotoxic effect of irinotecan.